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Interactions between iboga agents and methamphetamine sensitization: studies of locomotion and stereotypy in rats

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Abstract *Rationale:* The phenomenon of sensitization has been theoretically implicated in mediating various aspects of drug addiction. Recent dose-response studies demonstrated that pretreatment with the putative anti-addictive agent, ibogaine (IBO), and a synthetic iboga alkaloid congener, 18-methoxycoronaridine (18-MC), increase the potency of cocaine to elicit behavioral sensitization, an effect proposed to contribute, in part, to their ability to attenuate drug self-administration. *Objectives:* As abuse of the methylated amphetamine derivative, methamphetamine (METH), is a growing public health concern, the present study determined the interactions between IBO and 18-MC and the expression of METH-induced behavioral sensitization. *Methods:* The effects of pretreatment with 18-MC (40 mg/kg, IP, 19 h earlier) on the expression of METH-induced locomotion (0, 0.25, 0.5, 1 and 2 mg/kg, IP) and the effects of pretreatment with either IBO or 18-MC on the expression of METH-induced stereotypy (2 and 4 mg/kg, IP) were assessed in rats treated chronically with either METH (4 mg/kg daily for 7 days) or saline. *Results:* Compared to vehicle-pretreated controls, 18-MC produced an overall enhancement in METH-induced locomotion in rats treated chronically, but not acutely, with METH. In addition, both iboga agents increased the stereotypic response to METH. *Conclusions:* Iboga agents augment both the locomotor and stereotypic effects of METH in a manner consistent with previous reports for cocaine. Thus, it appears that iboga agents interact in a similar manner with the neural mechanisms mediating motor hyperactivity induced by the chronic administration of stimulant drugs.

Keywords Ibogaine · 18-Methoxycoronaridine · Methamphetamine · Locomotor activity · Stereotypy · Sensitization

Introduction

The repeated, intermittent, passive administration of many addictive substances (including cocaine, the amphetamines, ethanol, nicotine, morphine and heroin) can induce a progressive increase in, or sensitization of, certain behavioral effects of these drugs in laboratory rodents (for reviews, see Robinson and Berridge 1986; Kalivas and Stewart 1991; Kalivas et al. 1993; Stewart and Badiani 1993). Well-characterized changes in behavior include increases in locomotor hyperactivity, sniffing, gnawing, licking, paw nibbling, climbing, and rearing (e.g., Segal and Schuckit 1983; Robinson and Becker 1986; Kalivas et al. 1988; Mattingly and Gotsick 1989). Some current theories of drug addiction argue that the cellular neuroadaptations mediating behavioral sensitization are relevant to certain aspects of psychomotor stimulant addiction, for example, craving and psychosis (for discussions, see Robinson and Becker 1986; Robinson and Berridge 1993; Kalivas et al. 1998).

The repeated self-administration of addictive substances (including psychomotor stimulants and opiates) by laboratory rodents can induce the expression of sensitization of drug-induced locomotor hyperactivity (Schenk and Partridge 1997; DeVries et al. 1998; Vezina et al. 1999). In addition, the repeated self-administration of amphetamine can induce sensitization of extracellular levels of dopamine in the nucleus accumbens (Lorrain et al. 1999), which is implicated in mediating the augmented incentive motivational/rewarding effects of drugs of abuse in drug addiction (for discussion, see Robinson and Berridge 1993). Recently, Deroche et al. (1999) demonstrated that rats with 29 versus 6 cocaine self-administration sessions exhibited both a higher responsiveness to cocaine-induced reinstatement of bar-pressing behavior and a shorter latency to reach a goal box in which they received passive cocaine injections. These

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data were interpreted to indicate that rats with a longer history of cocaine self-administration exhibited sensitized motivation towards subsequent cocaine, compared to rats with a shorter cocaine self-administration history (Deroche et al. 1999). These effects were inversely proportional to the subsequent dose of cocaine administered, supporting clinical observations that the positive reinforcing effects of cocaine are inversely related to cocaine dose (Cohen 1973; Gold and Bowers 1978). The subjective effects of drugs abuse contribute significantly to their initial use and the maintenance of their administration (Jaffe 1992; de Wit 1998). In support of sensitization theories, clinical evidence indicates that, compared to less experienced drug users or drug-naïve individuals, drug addicts have augmented sensitivity to both the positive (Grant et al. 1996; Breiter et al. 1997; Liguori et al. 1997) and negative (Ellinwood 1968; Angrist 1983) reinforcing effects of psychomotor stimulant drugs. Consistent with this are reports of enhanced brain activity in regions innervated by the mesolimbic dopamine system, including the frontal cortex (Alper et al. 1999) and the amygdala (Childress et al. 1999) in cocaine addicts.

Given the evidence implicating the phenomenon of sensitization in the mediation of the addictive and psychotogenic properties of drugs of abuse, a series of experiments conducted by this laboratory have focused on characterizing the effects of pretreatment with the potential "anti-addictive" drugs, ibogaine (IBO; see Glick and Maisonneuve 1998; Popik and Skolnick 1999 for reviews), and a synthetic IBO derivative, 18-methoxycoronaridine (18-MC; see Glick et al. 1999, 2000 for reviews), on the expression of sensitization produced by several drugs of abuse. An early study demonstrated that IBO produced differential effects on the expression of amphetamine-induced locomotion, depending on the previous amphetamine history of the animal; IBO increased the acute locomotor response to amphetamine but attenuated the locomotor response to amphetamine in chronic amphetamine-treated male rats (Blackburn and Szumlinski 1997). As this finding was consistent with an IBO-induced decrease in morphine-induced locomotion in rats with prior morphine history (Pearl et al. 1995), it was postulated that IBO pretreatment reversed or reset the neuroadaptations underlying the expression of behavioral enhancement produced by the chronic administration of drugs of abuse (Blackburn and Szumlinski 1997). However, a recent study demonstrated that IBO enhances the expression of cocaine-induced locomotor sensitization (Szumlinski et al. 1999a) and this reflects a shift in the inverted U-shaped dose-effect curve for cocaine-induced locomotion to the left of vehicle (VEH) controls (Szumlinski et al. 1999b). Consistent with this, 18-MC was also found to augment the expression of cocaine-induced locomotion in female rats treated either acutely or chronically with cocaine (Szumlinski et al. 2000c). Both IBO and 18-MC enhance the stereotypy following acute or chronic cocaine administration (Szumlinski et al. 1999c). In combination, the results of these cocaine studies indicated that iboga agents increase an animal's

sensitivity to the behavioral-activating and sensitizing effects of cocaine.

As the expression of stimulant-induced stereotypic behaviors can be physically incompatible with locomotion (e.g., Glick 1972), the possibility existed that previous results (Blackburn and Szumlinski 1997) reflected an increase in the intensity of the behavioral effects of chronic amphetamine, rather than a reversal of these effects. As the methylated amphetamine derivative, methamphetamine (METH), produces virtually identical effects on motor behavior as does its parent compound (e.g., Kuczenski et al. 1995), the present study addressed this possibility by examining the effects of 18-MC pretreatment on the expression of locomotion induced by METH, in rats treated chronically with either saline (SAL) or METH. To determine whether the decrease in locomotion observed in past (Blackburn and Szumlinski 1997) and present studies reflected a relative increase in the stereotypic response to amphetamines, the effects of pretreatment with both IBO and 18-MC on the expression of METH-induced stereotypy were also determined.

Materials and methods

Subjects

Consistent with previous locomotor studies (Szumlinski et al. 1999b), female Sprague-Dawley rats (Taconic, Germantown, N.Y., USA), weighing 200–250 g at the beginning of the experiment, were housed in groups of four and allowed free access to food and water. In all, 120 rats were used in the locomotor study ($n=6$) and 48 rats were used in each stereotypy study ($n=6$). The animals were maintained on a 12-h light cycle (lights on at 0700 hours) in a room carefully controlled for heat (25°C) and humidity (25%). All testing began at approximately 1000 hours. For all animal experiments, the "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed.

Apparatus

Locomotion was studied in opaque, cylindrical (60 cm) photocell activity cages with three intersecting light beams. The photocells were located equidistantly from each other around the circumference of the cage, 3 cm above the floor. Each time a light beam was broken a single activity count was recorded by a 386 PC computer with Med Associates software. Stereotypy was observed in clear, ventilated, cylindrical (30 cm) Plexiglas cages with wire mesh floors. Clear Plexiglas lids were placed on top of the cages to prevent escape of the animals during the injection sessions.

Drugs

Methamphetamine hydrochloride (METH; Sigma Chemical Co.) was dissolved in saline (SAL) and injected IP at a volume of 1.0 ml/kg. In both the locomotor and stereotypy experiments 4 mg/kg METH was used for chronic treatment. For the locomotor study, test doses were 0, 0.25, 0.5, 1.0 and 2.0 mg/kg ($n=6$). For the stereotypy studies, 2.0 and 4.0 mg/kg METH was used ($n=6$). Ibogaine hydrochloride (IBO; 40 mg/kg; Sigma Chemical Co.) was dissolved in MilliQ water and (+/-) 18-methoxycoronaridine hydrochloride (18-MC; 40 mg/kg; Albany Molecular Research Inc., Albany, N.Y., USA) was dissolved in a 0.01 M NaPO₄ buffer (pH=6). Both iboga compounds and their vehicles (VEH) were injected IP at a volume of 2.0 ml/kg.

Table 1 Summary of the design and procedures of the locomotor and stereotypy experiments in this study. In all, 120 rats were tested in the locomotor activity study. In both the IBO and 18-MC stereotypy studies, 48 rats were used

Experiment	Chronic treatment	Pretreatment (19 h prior to test)	Doses of METH tested (mg/kg)
Locomotor activity (n=120)	4.0 mg/kg METH (n=60)	VEH (n=30) 40.0 mg/kg 18-MC (n=30)	0.0, 0.25, 0.5, 1.0 & 2.0 (n=6)
	SAL (n=60)	VEH (n=30) 40.0 mg/kg 18-MC (n=30)	
Stereotypy (n=48 for each study)	4.0 mg/kg METH (n=24)	VEH (n=12) 40.0 mg/kg IBO (n=12)	2.0 & 4.0 (n=6)
	SAL (n=24)	VEH (n=12) 40.0 mg/kg IBO (n=12)	
	4.0 mg/kg METH (n=24)	VEH (n=12) 40.0 mg/kg 18-MC (n=12)	
	SAL (n=24)	VEH (n=12) 40.0 mg/kg 18-MC (n=12)	

Table 2 For the measurement of METH-induced general stereotypy, rats were given a single score for each 15-s interval according to the following behavioral rating scale [adapted from Creese and Iversen (1972)]. For the measurement of METH-induced repetitive head movements, rats were given a single score for each 15-s interval according to the following behavioral rating scale [adapted from Ujike et al. (1992)]

Score	Behavior(s) observed
General stereotypy	
0	Asleep or still
1	Hyperlocomotion with normal exploration and normal pattern of sniffing
2	Hyperlocomotion with repetitive exploratory behavior, rearing or increased rate of sniffing
3	Discontinuous sniffing with periodic locomotor activity
4	Continuous compulsive sniffing without locomotion
Repetitive head movements	
0	No head movement
1	Normal head movement associated with normal exploration
2	Increased rate of head movement associated with hyperactivity
3	Discontinuous repetitive and stereotyped up-down head movement
4	Continuous stereotyped head movement with occasional breaks
5	Continuous and intense stereotyped head movement in one location

Design and procedure

Table 1 outlines the design and procedures used in the present study. In brief, rats received daily injections of either METH or SAL for 7 consecutive days. Behavior was monitored each day for 2 h either in activity cages (locomotor study) or manually by an experimenter (stereotypy studies). For the locomotor activity study, cumulative data were collected in 10-min bins by a computer; for the stereotypy studies, behavior was scored for 30 s, every 20 min following the chronic treatment/test injection or every 15 min following SAL injection). Prior to each chronic treatment injection, animals were injected with SAL and habituated to their respective testing cages for 30 min. Following the seventh chronic treatment injection, animals were withdrawn from chronic treatment for 1 week. On the last day of withdrawal, rats in each of the experiments were randomly assigned to receive a pretreatment injection of either an iboga agent or VEH. In a manner consistent with previous locomotor studies (see Szumlinski et al. 1999b), rats

received a pretreatment injection of IBO, 18-MC (both at 40 mg/kg) or VEH and then, 19 h later, were randomly assigned to test groups that received their respective test dose of METH. Behavior was monitored for 2 h.

Behavioral scoring

Two behavioral rating scales were employed in the monitoring of stereotypic behavior (see Table 2). The first rated general stereotypy (GS) (Creese and Iversen 1972) and the second rated repetitive head movements (RHM) (Ujike et al. 1992). On every second injection day (i.e., injections 1, 3, 5 and 7), rats were observed for 15 s, at repeated intervals, beginning immediately following injection until the completion of the session. Observations were made either every 15 min for habituation sessions (total of three observation periods) or every 20 min for METH injection sessions (total of seven observation periods for chronic treatment and test

days). Rats were given a single score for each 15-s observation period. The observer was blind to the pretreatment of the animals on test days.

Statistical analysis

Data were examined for main effects by analysis of variance (ANOVA) for Chronic treatment (METH versus SAL), Injection number (1–7), Pretreatment (IBO, 18-MC or VEH), Time (twelve 10-min bins or seven 20-min bins), and Test dose (0, 0.25, 0.5, 1.0, 2.0 or 4.0 mg/kg METH). If there were significant effects, the data were decomposed and Duncan multiple range post-hoc tests were performed (Statistica).

Results

Chronic METH induced locomotor sensitization

As depicted in Fig. 1 (top), the responses of both chronic treatment groups to repeated SAL habituated across the 30-min SAL sessions [$F(\text{Injection number})6,708=92.84$, $P<0.0001$]. Chronic METH rats displayed elevated spontaneous locomotor activity from injections 2–7, compared to chronic SAL rats, indicating the presence of conditioned locomotor hyperactivity in METH-treated rats [$F(\text{Chronic treatment})1,118=45.18$, $P<0.0001$; $F(\text{Chronic treatment} \times \text{Injection number})6,708=14.69$, $P<0.0001$; post-hoc tests]. As depicted in Fig. 1 (bottom), chronic METH administration induced a sensitization of locomotor behavior by injection 5 of chronic treatment which persisted for the remainder of the chronic treatment phase of the study [$F(\text{Chronic treatment})1,118=65.56$, $P<0.0001$; $F(\text{Chronic treatment} \times \text{Injection number})6,708=11.67$, $P<0.0001$; post-hoc tests].

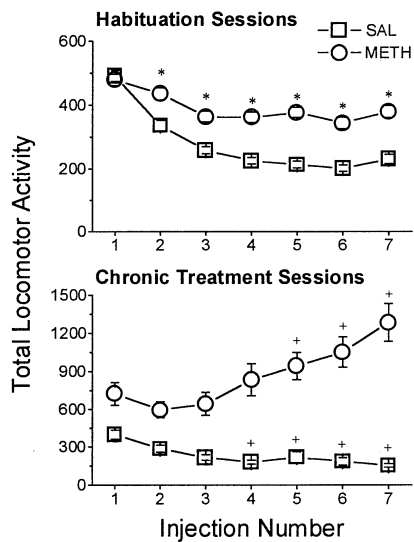


Fig. 1 Top: total locomotor activity of animals during the 30-min habituation sessions conducted prior to each chronic treatment session. Bottom: effects of daily chronic treatment with either SAL (squares) or 4.0 mg/kg METH (circles) on the total locomotor activity of the animals during each 2-h injection session. Each point represents the mean total number of photocell beam breaks ($\pm$ SEM) of 60 rats. * $P<0.05$ compared to SAL, + $P<0.05$, compared to injection 1 (Duncan's multiple range post-hoc tests)

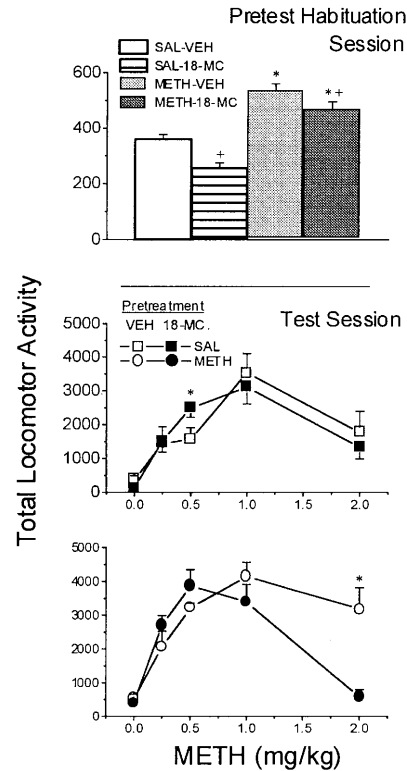


Fig. 2 Top: effects of pretreatment (18.5 h earlier) with 18-MC (40 mg/kg IP) or VEH on the total locomotor activity expressed by rats treated chronically with either SAL or METH (7×4.0 mg/kg) during the 30-min habituation sessions preceding the METH test. Each bar represents the mean total number of photocell beam breaks ($\pm$ SEM) of 30 rats. Middle and bottom: effects of pretreatment (19 h earlier) with 18-MC (40 mg/kg, IP; solid) or VEH (open) on the total locomotor activity expressed by rats treated chronically with either SAL (middle) or METH (7×4.0 mg/kg; bottom) in response to a challenge injection of METH (0.0, 0.25, 0.5, 1.0 and 2.0 mg/kg) during the 2-h test session. For middle and bottom, each point represents the mean total number of photocell beam breaks ($\pm$ SEM) of six rats. * $P<0.05$, compared to respective SAL; + $P<0.05$, compared to respective VEH (Duncan's multiple range post-hoc tests)

As depicted in Fig. 2 (top), rats chronically treated with METH displayed higher levels of locomotor activity to the SAL injection during the 30-min pretest habituation period, compared to chronic SAL-treated rats [$F(\text{Chronic treatment})1,116=82.82$, $P<0.0001$]. These results indicate that conditioned locomotor activity to METH was still present on test day. Overall, 18-MC pretreatment (40 mg/kg, 18.5 h earlier) lowered the spontaneous locomotion of animals during the SAL session [$F(\text{Pretreatment})1,116=15.16$, $P<0.0002$], indicating that 18-MC does not interact specifically with conditioned motor behavior.

METH (0, 0.25, 0.5, 1.0 and 2.0 mg/kg) dose-dependently induced the expression of locomotor behavior in both acute and chronic METH rats [$F(\text{Dose})4,100=37.08$, $P<0.0001$] (Fig. 2, bottom). As depicted in Fig. 2 (compare open symbols), chronic METH treatment induced the expression of sensitization in VEH controls as evidenced by a shift upwards in the dose-response curve

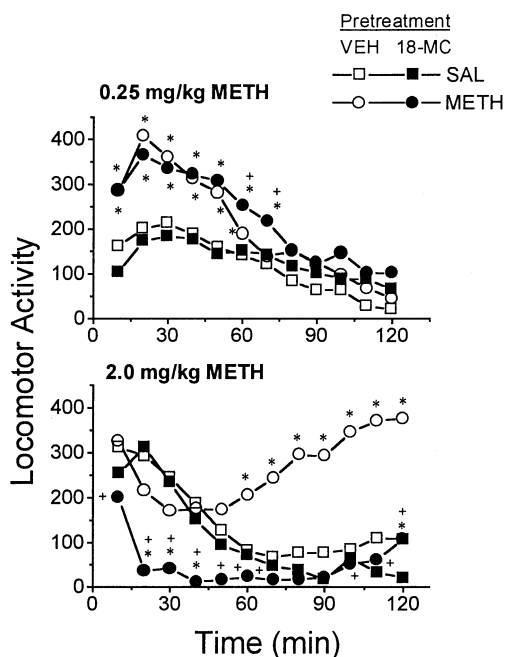


Fig. 3 Effect of pretreatment with 18-MC (40 mg/kg, 19 h earlier; solid) or VEH (open) on the time course of locomotor activity in response to the lowest and highest test doses of METH (0.25 and 2.0 mg/kg, respectively) in rats chronically treated with either SAL (squares) or METH (7×4.0 mg/kg; circles) during the 2-h test session. Each data point represents the mean number of photocell beam breaks of six rats at the indicated times after METH injection. Error bars are omitted for clarity. * $P < 0.05$, compared to respective SAL; + $P < 0.05$, compared to respective VEH (Duncan's multiple range post-hoc tests)

for METH-induced locomotion in chronic METH rats, compared to SAL rats [$F(\text{Chronic treatment})_{1,50} = 10.18$, $P < 0.003$]. As can be observed in Fig. 2 (compare open and closed symbols), pretreatment with 18-MC (40 mg/kg, 19 h earlier) altered the dose-response curve for total locomotion of VEH controls in rats treated chronically (bottom) [$F(\text{Pretreatment} \times \text{Dose})_{4,50} = 6.33$, $P < 0.0004$], but not acutely (middle) [$F(\text{Pretreatment} \times \text{Dose})_{4,50} = 0.97$, $P = 0.45$], with METH.

As the locomotor response to METH is triphasic (Segal and Kuczenski 1997), the effects of 18-MC on the time course of locomotion induced by the various doses of METH were determined. 18-MC pretreatment significantly altered the time course of METH-induced locomotion, an effect which depended on the previous METH history of the animals [$F(\text{Chronic treatment} \times \text{Pretreatment} \times \text{Dose} \times \text{Time})_{44,1089} = 1.62$, $P < 0.007$]. As can be observed in Fig. 3, 18-MC produced marginal effects on the time course of locomotion in rats treated chronically with SAL [$F(\text{Pretreatment} \times \text{Dose} \times \text{Time})_{44,550} = 1.34$, $P = 0.07$]. In contrast, 18-MC advanced the onset of both the early and late locomotor-activating effects and the locomotor-inactivating effects of METH in rats chronically treated with METH [$F(\text{Pretreatment} \times \text{Dose} \times \text{Time})_{44,550} = 4.86$, $P < 0.0001$; post-hoc tests].

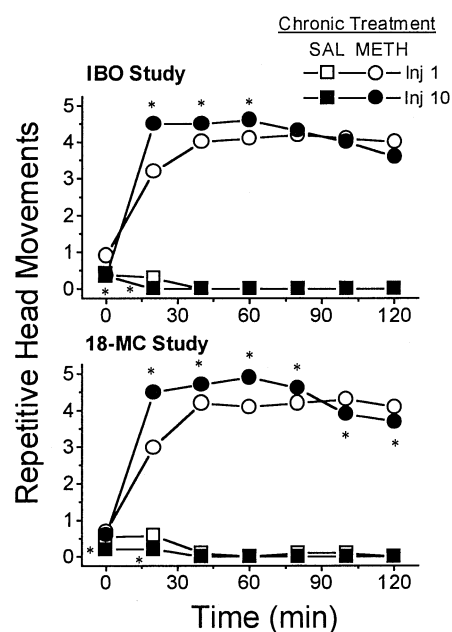


Fig. 4 Effects of daily chronic treatment with either saline (squares) or 4 mg/kg METH (circles) on the time courses of RHM expressed by rats on injection 1 of chronic treatment (open) versus injection 7 of chronic treatment (closed). Each point represents the mean total stereotypy score of 72 rats. Error bars were omitted for clarity. * $P < 0.05$ compared to injection 1 (Duncan's multiple range post-hoc tests)

Chronic METH-induced sensitization of stereotypy

Virtually identical results were observed for both the measures of general stereotypy (GS) and repetitive head movements (RHM) in the two experiments. Thus, the results of the statistical analyses of both measures are presented in the text, but only the data for RHM are presented in graphic form.

The expression of spontaneous GS and spontaneous RHM habituated across chronic treatment in both the IBO and 18-MC experiments (data not shown) [for GS: IBO, $F(\text{Injection number})_{3,132} = 42.42$, $P < 0.0001$; 18-MC, $F(\text{Injection number})_{3,138} = 52.93$, $P < 0.0001$; for RHM: IBO, $F(\text{Injection number})_{3,132} = 93.30$, $P < 0.0001$; 18-MC, $F(\text{Injection number})_{3,138} = 103.28$, $P < 0.0001$]. No evidence for conditioned stereotyped behavior was observed in rats chronically treated with METH (7×4 mg/kg) for either experiment [for GS: IBO, $F(\text{Chronic treatment} \times \text{Injection number})$, $P = 0.79$; 18-MC, $F(\text{Interaction})$, $P = 0.58$; for RHM: IBO, $F(\text{Interaction})$, $P = 0.06$; 18-MC, $F(\text{Interaction})$, $P = 0.64$].

As can be observed in Fig. 4, in both studies, the latency to peak stereotypic effects decreased from injection 1 to injection 7 of chronic treatment in rats treated chronically with METH, whereas the stereotypy expressed by chronic SAL animals habituated [for GS: IBO, $F(\text{Chronic treatment} \times \text{Injection number} \times \text{Time})$]

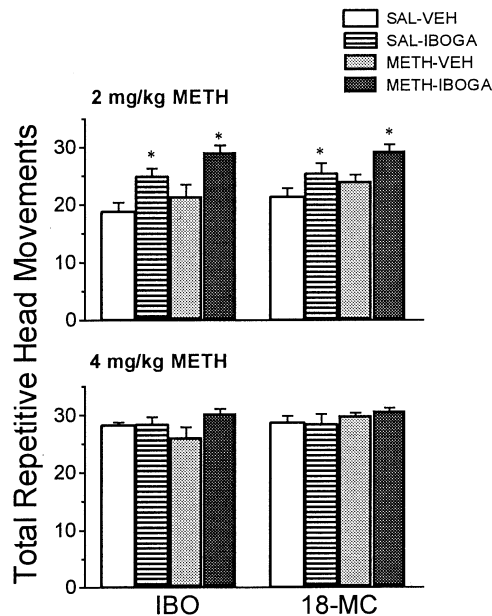


Fig. 5 Effects of pretreatment (19 h earlier) with either IBO or 18-MC (40 mg/kg, IP) (left and right of each graph, respectively) on the total scores for repetitive head movements (RHM) in response to a challenge injection of either 2.0 or 4.0 mg/kg METH (top and bottom, respectively) during the 2-h test session. Each bar represents the mean total score for RHM ($\pm$ SEM) of six rats. * $P < 0.05$, compared to respective VEH group (Duncan's multiple range post-hoc tests)

6,264=6.52, $P < 0.0001$; 18-MC, $F(\text{Interaction})_{6,276} = 5.74$, $P < 0.0001$; for RHM: IBO, $F(\text{interaction})_{6,264} = 11.77$, $P < 0.0001$; 18-MC, $F(\text{Interaction})_{6,276} = 10.84$, $P < 0.0001$; post-hoc tests]. Thus, sensitization of both GS and RHM was produced by chronic METH administration in both studies.

18-MC and IBO enhanced METH-induced stereotypy

During the 30-min pre-test habituation session, no evidence of conditioned sensitization was apparent in the chronic METH-treated rats [for GS: IBO, $F(\text{Chronic treatment})$, $P = 0.72$; 18-MC, $F(\text{Chronic treatment})$, $P = 0.50$; for RHM: IBO, $F(\text{Chronic treatment})$, $P = 0.47$; 18-MC, $F(\text{Chronic treatment})$, $P = 0.73$]. Overall, prior iboga pretreatment (40 mg/kg, 18.5 h earlier) did not significantly alter the spontaneous expression of stereotypy in either experiment, although a marginal decrease in stereotypy was observed in the IBO experiment [for GS: IBO, $F(\text{Pretreatment})$, $P = 0.51$; 18-MC, $F(\text{Pretreatment})$, $P = 0.50$; for RHM: IBO, $F(\text{Pretreatment})$, $P = 0.06$; 18-MC, $F(\text{Pretreatment})$, $P = 0.49$] (data not shown).

In both experiments, METH (2.0 and 4.0 mg/kg) produced dose-dependent effects on both stereotypy variables [for GS: IBO, $F(\text{Dose})_{1,38} = 12.91$, $P < 0.001$; 18-MC, $F(\text{Dose})_{1,40} = 5.70$, $P < 0.03$; for RHM: IBO, $F(\text{Dose})_{1,38} = 23.36$, $P < 0.0001$; 18-MC, $F(\text{Dose})_{1,40} = 24.49$, $P < 0.0001$]. As is evident from Fig. 5, no sensitization of stereotypy was observed in VEH controls on test day [for GS: IBO, $F(\text{Chronic treatment})_{1,18}$,

$P = 0.31$; 18-MC, $F(\text{Chronic treatment})_{1,20}$, $P = 0.62$; for RHM: IBO, $F(\text{Chronic treatment})_{1,18}$, $P = 0.55$; 18-MC, $F(\text{Chronic treatment})_{1,20}$, $P = 0.09$]. Pretreatment with either iboga agent increased the total scores for GS and RHM in response to 2.0 mg/kg test dose only [for GS: IBO, $F(\text{Pretreatment})_{1,38} = 22.20$, $P < 0.0001$; $F(\text{Pretreatment} \times \text{Dose})_{1,38} = 6.34$, $P < 0.02$; 18-MC, $F(\text{Pretreatment})_{1,40} = 5.70$, $P < 0.03$; $F(\text{Pretreatment} \times \text{Dose})_{1,40} = 5.70$, $P < 0.03$; for RHM: IBO, $F(\text{Pretreatment})_{1,38} = 20.80$, $P < 0.001$; $F(\text{Pretreatment} \times \text{Dose})_{1,38} = 5.57$, $P < 0.03$; 18-MC, $F(\text{Pretreatment})_{1,40} = 7.85$, $P < 0.008$; $F(\text{Pretreatment} \times \text{Dose})_{1,40} = 6.36$, $P < 0.02$] (post-hoc tests).

As 18-MC pretreatment significantly altered the time course of METH-induced locomotion, the effects of iboga pretreatment on the time course of stereotypy were determined. IBO prolonged the duration of the GS and RHM effects of METH at later times during the 2-h test session [for GS: $F(\text{Pretreatment} \times \text{Time})_{6,228} = 3.60$, $P < 0.002$; for RHM: $F(\text{Pretreatment} \times \text{Time})_{6,228} = 6.30$, $P < 0.0001$] and similar effects of 18-MC were observed for RHM [$F(\text{interaction})_{6,240} = 3.15$, $P < 0.04$], but not for GS [$F(\text{interaction})$, $P = 0.71$] (data not shown).

Discussion

Consistent with previous studies of the effects of iboga agents on cocaine-induced locomotion (e.g., Maisonneuve and Glick 1992; Szumlinski et al. 1999a, 1999b, 2000b, 2000c), pretreatment with the novel, synthetic iboga alkaloid, 18-MC (40 mg/kg, 19 h earlier), enhanced the expression of locomotor activity in response to the methylated amphetamine derivative, METH, in rats sensitized by repeated METH administration. Compared to sensitized VEH controls, 18-MC enhanced the locomotor response to lower METH doses and attenuated the locomotor response to higher METH doses. This enhancement by pretreatment with 18-MC was not observed in rats treated acutely with METH. Also consistent with previous cocaine studies (e.g., Szumlinski et al. 1999a, 2000c), 18-MC selectively altered the time course of locomotor activity in rats treated repeatedly with METH, further indicating that the effects of iboga agents on both the locomotor-activating and locomotor-inhibiting effects of stimulants are greater in rats with previous stimulant history. Consistent with the hypothesis that iboga agents produce a general enhancement of the behavioral-activating and/or sensitizing effects of amphetamines, pretreatment with both IBO and 18-MC (both at 40 mg/kg, 19 h earlier) augmented the stereotypy induced by a high dose of METH (2.0 mg/kg) in both acute and chronic METH-treated rats. Thus, the present results indicate that the locomotor-attenuating effects of iboga pretreatment observed at higher doses of amphetamines in rats chronically treated with amphetamines (Blackburn and Szumlinski 1997; present study) are attributable to the induction of maximal levels of stereotypic behavior and not a selective attenuation of amphetamine-induced behavior in chronic amphetamine-treated rats.

The present study extends previous indications that the effects of iboga agents on stimulant-induced behavioral sensitization (Szumlinski et al. 1999a, 1999b, 1999c, 2000b, 2000c) can be dissociated from their ability to decrease the self-administration of stimulants (e.g., Cappendijk and Dzoljic 1993; Glick et al. 1994, 1996a, 1996b). We suggested previously (e.g., Maisonneuve and Glick 1992; Szumlinski et al. 1999b) that the "anti-addictive" effects of iboga agents with respect to stimulant self-administration may be related to their ability to increase sensitivity to the behavioral and perhaps, psychotogenic (Cohen 1972; Gold and Bowers 1978), properties of stimulant drugs. Although it is clear from both past and present studies that iboga pretreatment augments the stereotypic effects of stimulant drugs, this effect cannot account entirely for the effects of these compounds on drug self-administration behavior; iboga pretreated animals still respond for stimulants in self-administration paradigms, but do so more infrequently than controls (e.g., Glick and Maisonneuve 1998). Secondly, the results of microdialysis studies conducted in our laboratory (Pearl et al. 1996; Szumlinski et al. 2000a, 2000b, 2000c) demonstrate that iboga agents consistently reverse the expression of sensitized extracellular levels of dopamine in the nucleus accumbens. These data contradict our increased sensitivity hypothesis as the sensitization of accumbal dopamine transmission is putatively implicated in mediating the psychotogenic effects of stimulant drugs (e.g., Robinson and Becker 1986). Given the putative role for accumbal dopamine in mediating the rewarding/incentive motivational effects of drugs (Fibiger and Phillips 1986; Wise and Bozarth 1987; Koob 1992; Kalivas et al. 1993; Robinson and Berridge 1993; Berridge and Robinson 1998), we suggest, instead, that iboga agents exert their effects on drug self-administration by reversing the enhanced incentive motivation to self-administer drugs produced by chronic drug administration. In support of this hypothesis, a recent morphine self-administration study demonstrated that 18-MC pretreatment shifts the dose-response function for morphine self-administration downwards, indicating that 18-MC can decrease the reinforcing efficacy of morphine in self-administering rats (Maisonneuve and Glick 1999).

In conclusion, pretreatment with the synthetic iboga alkaloid congener, 18-MC, decreases the latency to onset of the locomotor-activating effects of METH, an effect that is greater in rats with previous METH experience. 18-MC pretreatment also decreases the latency to onset and increases the duration of the attenuating effects of METH on locomotion. This effect is attributed to an enhancement of METH-induced stereotypy. These results demonstrate that iboga pretreatment increases sensitivity to the behavioral effects of an amphetamine in rats treated chronically or acutely with an amphetamine, extending previous results with another psychomotor stimulant and drug of abuse, cocaine.

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References

- Alper KR (1999) The EEG and cocaine sensitization: a hypothesis. *J Neuropsychiatr Clin Neurosci* 11:209–211
- Angrist B (1983) Psychosis induced by central nervous system stimulants and related drugs. In: Cresse I (ed) *Stimulants: neurochemical, behavioral and clinical perspectives*. Raven Press, New York, pp 1–30
- Berridge KC, Robinson TE (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res Rev* 28:309–369
- Blackburn JR, Szumlinski KK (1997) Ibogaine effects on sweet preference and amphetamine-induced locomotion: implications for drug addiction. *Behav Brain Res* 89:99–106
- Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hymen SE (1997) Acute effects of cocaine on human brain activity and emotion. *Neuron* 19:591–611
- Cappendijk SLT, Dzoljic MR (1993) Inhibitory effects of ibogaine on cocaine self-administration in rats. *Eur J Pharmacol* 241:261–265
- Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP (1999) Limbic activation during cue-induced cocaine craving. *Am J Psychiatry* 156:11–18
- Cohen S (1975) Cocaine. *JAMA* 231:74–75
- Creese I, Iversen SD (1972) Amphetamine response in rat after dopamine neuron destruction. *Nature New Biol* 238:247–248
- Deroche V, Le Moal M, Piazza PV (1999) Cocaine self-administration increases the incentive motivational properties of the drugs in rats. *Eur J Neurosci* 11:2731–2736
- De Vries TJ, Schoffelmeier ANM, Binnekade R, Mulder AH, Vanderschuren LJMJ (1998) Drug-induced reinstatement of heroin- and cocaine-seeking behaviour following long-term extinction is associated with expression of behavioural sensitization. *Eur J Neurosci* 10:3565–3571
- de Wit H (1998) Individual differences in acute effects of drugs in humans: their relevance to risk for abuse. *NIDA Res Mongr* 169:176–187
- Ellinwood EH (1968) Amphetamine psychosis. II. Theoretical implications. *J Neuropsychiatr* 4:45–54
- Fibiger HC, Phillips AG (1986) Reward, motivation, cognition: psychobiology of mesotelencephalic dopamine systems. In: Mountcastle VB, Bloom FE, Geiger SR (eds) *Handbook of physiology: the nervous system*, vol 4. American Physiological Society, Bethesda, Md., pp 647–675
- Glick SD (1972) Changes in amphetamine sensitivity following frontal cortical damage in rats and mice. *Eur J Pharmacol* 20:351–356
- Glick SD, Maisonneuve IM (1998) Mechanisms of anti-addictive actions of ibogaine. *Ann NY Acad Sci* 844:214–226
- Glick SD, Kuehne ME, Raucci J, Wilson TE, Larson D, Keller Jr. RW, Carlson JN (1994) Effects of iboga alkaloids on morphine and cocaine self-administration in rats: relationship to tremorigenic effects and to effects on dopamine release in nucleus accumbens and striatum. *Brain Res* 657:14–22
- Glick SD, Kuehne ME, Maisonneuve IM, Bandarage UK, Molinari HH (1996a) 18-Methoxycoronaridine, a non-toxic iboga alkaloid congener: effects on morphine and cocaine self-administration and on mesolimbic dopamine release in rats. *Brain Res* 719:29–35
- Glick SD, Pearl SM, Cai J, Maisonneuve IM (1996b) Ibogaine-like effects of noribogaine in rats. *Brain Res* 713:294–297
- Glick SD, Maisonneuve IM, Hough LB, Kuehne ME, Bandarage UK (1999) (±)-18-Methoxycoronaridine: a novel iboga alkaloid congener having potential anti-addictive efficacy. *CNS Drug Rev* 5:27–42
- Glick SD, Maisonneuve IM, Szumlinski KK (2000) 18-Methoxycoronaridine (18-MC) and ibogaine: comparison of anti-addictive efficacy, toxicity and mechanisms of action. *Ann NY Acad Sci* (in press)
- Gold MS, Bowers MB (1978) Neurobiological vulnerability to low-dose amphetamine psychosis. *Am J Psychiatry* 135:1546–1548

- Grant S, London ED, Newlin DB, Willemange VL, Liu X, Contoraggi C, Phillips RL, Kimes AS, Margolin A (1996) Activation of memory circuits during cue-elicited cocaine craving. *Proc Natl Acad Sci USA* 93:12040–12045
- Jaffe (1992) Current concepts of addiction. In: O'Brien CP, Jaffe JH (eds) *Addictive states*. Raven Press, New York
- Kalivas PW, Stewart J (1991) Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Res Rev* 16:223–244
- Kalivas PW, Duffy P, DuMars LA, Skinner C (1988) Behavioral and neurochemical effects of acute and daily cocaine administration in rats. *J Pharmacol Exp Ther* 245:485–492
- Kalivas PW, Sorg BA, Hooks, MS (1993) The pharmacology and neural circuitry of sensitization to psychostimulants. *Behav Pharmacol* 4:315–334
- Kalivas PW, Pierce RC, Cornish J, Sorg BA (1998) A role for sensitization in craving and relapse in cocaine addiction. *J Psychopharmacol* 12:49–53
- Koob GF (1992) Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol Sci* 13:177–184
- Kuczenski R, Segal DS, Cho AK, Melega W (1995) Hippocampus norepinephrine, caudate dopamine and serotonin, and behavioral response to the stereoisomers of amphetamine and methamphetamine. *J Neurosci* 15:1308–1317
- Liguori A, Hughes JR, Goldberg K, Callas P (1997) Subjective effects of oral caffeine in formerly cocaine-dependent humans. *Drug Alcohol Depend* 49:17–24
- Lorrain DS, Austin JD, Arnold GM, Vezina P (1999) Rats pre-exposed to amphetamine will subsequently work more to obtain the drug and show enhanced DA overflow in the NAcc. *Soc Neurosci Abstr* 25:1820
- Maisonnette IM, Glick SD (1992) Interactions between ibogaine and cocaine in rats: in vivo microdialysis and motor behavior. *Eur J Pharmacol* 212:263–266
- Maisonnette IM, Glick SD (1999) Attenuation of the reinforcing efficacy of morphine by 18-methoxycoronaridine. *Eur J Pharmacol* 383:15–21
- Mattingly BA, Gotsick JE (1989) Conditioning and experimental factors affecting the developments of sensitization to apomorphine. *Behav Neurosci* 103:1311–1317
- Pearl SM, Johnson DW, Glick SD (1995) Prior morphine exposure enhances ibogaine antagonism of morphine-induced locomotor stimulation. *Psychopharmacology* 121:470–475
- Pearl SM, Maisonnette IM, Glick SD (1996) Prior morphine exposure enhances ibogaine antagonism of morphine-induced dopamine release in rats. *Neuropharmacology* 35:1779–1784
- Popik P, Skolnick, P (1999) Pharmacology of ibogaine and ibogaine-related alkaloids. In: *The alkaloids*. Academic Press, New York, pp 197–231
- Robinson TE, Becker JB (1986) Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res Rev* 396:57–198
- Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of drug addiction. *Brain Res Rev* 18:247–291
- Schenk S, Partridge B (1997) Sensitization and tolerance in psychostimulant self-administration. *Pharmacol Biochem Behav* 57:543–550
- Segal DS, Kuczenski R (1997) Repeated binge exposures to amphetamine and methamphetamine: behavioral and neurochemical characterization. *J Pharmacol Exp Ther* 282:561–573
- Segal DS, Schuckit MA (1983) Animal models of stimulant-induced psychosis. In: Creese I (ed) *Stimulants: neurochemical, behavioral and clinical perspectives*. Raven Press, New York, pp 131–167
- Stewart J, Badiani A (1993) Tolerance and sensitization to the behavioral effects of drugs. *Behav Pharmacol* 4:289–312
- Szumliński KK, Maisonneuve IM, Glick SD (1999a) Ibogaine enhances the expression of cocaine-induced locomotor sensitization in chronic cocaine-treated animals. *Pharmacol Biochem Behav* 63:457–464
- Szumliński KK, Maisonneuve IM, Glick SD (1999b) Pretreatment with the putative anti-addictive drug, ibogaine, increases the potency of cocaine to elicit locomotor responding: a study with acute and chronic cocaine-treated rats. *Psychopharmacology* 145:227–233
- Szumliński KK, Maisonneuve IM, Glick SD (1999c) Iboga agents enhance the expression of cocaine-induced stereotypy in acute and chronic cocaine-treated rats. *Behav Pharmacol* 10:S92
- Szumliński KK, Maisonneuve IM, Glick SD (2000a) The potential anti-addictive agent, 18-methoxycoronaridine (18-MC) blocks the sensitized dopamine and locomotor responses produced by repeated morphine treatment. *Brain Res* 864:13–23
- Szumliński KK, Maisonneuve IM, Glick SD (2000b) Differential effects of ibogaine on behavioural and dopamine sensitization. *Eur J Pharmacol* (in press)
- Szumliński KK, McCafferty CA, Maisonneuve IM, Glick SD (2000c) Interactions between 18-methoxycoronaridine (18-MC) and cocaine: dissociation of behavioural and neurochemical sensitization. *Brain Res* (in press)
- Ujike H, Kanzaki A, Okumura K, Akiyama K, Otsuki S (1992) Sigma (σ) antagonist BMY 14802 prevents methamphetamine-induced sensitization. *Life Sci* 50:PL129–PL134
- Vezina P, Arnold GM, Lorrain DS (1999) Rats pre-exposed to amphetamine in the ventral tegmental area, but not in the nucleus accumbens, will subsequently work more to obtain the drug. *Soc Neurosci Abstr* 25:1820
- Wise RA, Bozarth MA (1987) A psychomotor stimulant theory of addiction. *Psychol Rev* 94:469–492